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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/722,659	09/27/96	BENNETT	D	104385.140

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EXAMINER	
EWOLDT,G	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/722,659	Applicant(s) Bennett et al.
	Examiner Gerald Ewoldt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *May 23, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-7, 18, and 19* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7, 18, and 19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Dr. Gerald Ewoldt, Art Unit 1644.

2. Applicant's amendment, filed 5/23/00, is acknowledged.

3. Claims 1-7 and 18-19 are pending and being acted upon.

4. In view of Applicant's amendment and response, filed 5/23/00, all previous rejections made under 35 U.S.C. § 112 first and second paragraphs have been withdrawn. Only the following rejections remain.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.
> (f) he did not himself invent the subject matter sought to be patented.

6. Claims 1-7 and 18-19 are rejected under 35 USC 102(e) or (f) over U.S. Patent No. 5,997,863 filed July 8, 1994. The inventive entity of U.S. Patent No. 5,997,863 has inventors in common with the instant application but is not the same inventive entity as that of the instant application. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 USC 102(e). This rejection under 35 USC 102(e) might be overcome either by showing under 37 CFR 1.132 that any invention of this invention disclosed but not claim in the reference was derived from the inventor of this application and is thus not the invention "by another" or an appropriate showing under CFR 1.131.

The '863 patent teaches a method of treating ischemia in a rabbit hind limb ischemic model by administering heparinase 1 (see column 8, line 62 through claim 18, line 34, in particular). The '863 patent also discloses that administering heparinase releases heparin binding growth factors and degrading components of the extracellular matrix, thereby facilitating the mobility of cytokines, chemoattractants and cells (see column 6, lines 25-59, in particular). The '863 patent further discloses that wound healing is generally divided into three temporally overlapping phases, inflammation, proliferation and remodeling. During inflammation, blood borne cells infiltrate the wound site and release mediating factors (see column 2, lines 56-67, in particular). The instant specification on page 39 teaches that ischemia induces inflammatory responses such as migration of neutrophils across the connective tissue, extravasation of plasma and other blood and cellular components. Therefore, the method of treating ischemia by administering

heparinase taught by the '863 patent would also decrease the localized inflammatory responses that result from ischemia. Thus, the methods of '863 patent anticipate the instantly claimed method of decreasing localized inflammatory responses.

Applicant's arguments have been fully considered but have not been found persuasive, essentially for the same reasons set forth in Paper No. 19. Applicant argues that the '863 patent does not teach a method of decreasing a localized inflammatory response by the administration of heparinase but rather a method of promoting revascularization (and thus wound healing) by the administration of heparinase. However, the heading of Example 8 is entitled "Evaluation of Local Administration of Heparinase to Enhance Revascularization", thus indicating a localized treatment for a localized response. Further, Table 4 is entitled "Treatment of ischemic hind limb", thus establishing a treatment of ischemia. In addition, the '863 patent teaches that the administration of heparinase intravascularly could be used as a treatment following a surgical procedure (column 13 paragraph 3), or for treatment of vessels in ischemic regions (column 13 paragraph 4). Clearly, the method of enhancing wound healing of the '863 patent encompasses the method of treating ischemia/reperfusion injury of the instant claims. One of ordinary skill in the art could not say when or where the administration of heparinase, after for example organ transplant, ceased being a treatment for ischemia/reperfusion injury and began being a treatment for wound healing.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-7 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogewerf et al., (W) (J. Biol. Chem 270:3268, February, 1995), Gilat et al., (X)(J. Exp. Med. 181:1929, May, 1995), Vlodavsky et al., (AA) (Invasion Metastasis 12: 112, 1991), U.S. Patent No. 5,169,722 (issued Dec. 8, 1992), U.S. Patent No. 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991), and U.S. Patent No. 5,567,417 (issued October 22, 1996, priority to November 17, 1993) in view of Nash et al. (J. of Pharm. and Exp. Ther. 274:1463, 1995), Lider et al. (Y)(P.N.A.S. 92:5037, May 1995), or Gilat et al. (AA) (J. Immunol. 153:4899, 1994).

The claims are directed to methods of treating localized inflammatory responses by administering heparinase enzymes. Claim 6 recites a limitation wherein the heparinase enzyme is expressed from a recombinant nucleotide sequence in *Flavobacterium heparinum*. Claim 7 recites a limitation wherein the heparinase enzyme is expressed from a recombinant nucleotide sequence in an organism in which it does not naturally occur.

Hoogewerf et al. teaches a pharmaceutical composition comprising heparinase enzyme obtained from human platelets (see abstract and page 3269, in particular).

Gilat et al. (1995) teaches a pharmaceutical composition comprising a heparinase enzyme obtained from human placenta (see pages 1929-1930, in particular).

Vlodavsky et al. teaches a heparinase enzyme, heparitinase. The heparitinase enzyme taught by Vlodavsky et al. is encompassed by the claim language since the specification discloses on page 14, lines 19-33 that heparinase enzyme is an enzyme that degrades heparin.

The '772 patent discloses heparinase enzymes expressed by *Flavobacterium heparinum* and a method of producing heparinase enzyme recombinantly in an organism in which it does not naturally occur (see column 3, line 26 through column 6, line 16, and column 8 line 4 through column 10 and claims 1-2, in particular).

The '641 patent discloses purified heparinase obtained from human SK-HEP-1 in a pharmaceutical composition (see column 12, line 59 through column 16, line 54 and claims 1-39, in particular). The '641 patent further teaches that FGF is released by addition of heparinase to extracellular matrix (ECM) which promotes wound healing. Wound healing is a facet of inflammation. The '641 patent also discloses but does not exemplify that administration of heparinase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and peripheral ischemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular).

The '417 patent discloses pharmaceutical compositions for delivering an effective dose of heparinase (see column 8, line 29 through column 11, line 7 and Claims 1 in particular). The '417 patent also discloses that the heparinase may be administered in composition comprising biodegradable polymeric matrices or liposomes (see Claims 4 and 8, column 16, lines 17-27, in particular). The '417 patent discloses three heparin enzymes produced by *Flavobacterium heparinum*. The '417 patent further discloses that Heparinases I and III inhibits both neovascularization *in vivo* and proliferation of capillary endothelial cells mediated by fibroblast growth factor in vitro. The '417 patent also teaches that Heparinase II did not inhibit neovascularization *in vivo*, but is useful in the alteration of smooth muscle cell proliferation (see column 3, line 33 through column 4, line 39, in particular). The '417 patent further discloses but does not exemplify the use of heparinase to treat disease in which neovascularization plays a prominent role such as rheumatoid arthritis and eye diseases such as diabetic retinopathy, neovascular glaucoma, and inflammatory eye disease see column 1, line 47 through column 2, line 25, in particular).

Hoogewerf et al., Gilat et al, Vlodavsky et al. and the '772 patent do not teach the use of the heparinase enzymes to treat inflammatory responses or that heparinase enzyme decreases accumulation of leukocytes or inhibits leukocyte extravasation. However, the limitations recited in Claims 2-5 are properties of the heparinase enzymes.

Nash et al. teaches that angiogenesis is required for the progression of chronic inflammation and agents that alter it can affect the development of inflammation and the consequent tissue destruction (see abstract, in particular).

Lider et al. teach that heparinase inhibits secretion of TNFα and that TNFα is a major mediator in T cell mediated inflammatory responses.

Gilat et al.(AA) (1994) teaches that heparinases degrade heparin from ECM which leads to the release of cytokines which leads to leukocytes becoming mobile (see particularly page 4909, column 1, paragraph 1).

The '641 and '417 patents disclose but do not exemplify administration of heparinases to treat localized inflammatory responses in a variety of diseases including cerebral and peripheral ischemic disease, diabetes, systemic lupus, inflammatory eye disease and rheumatoid arthritis.

Therefore it would have been obvious to one with ordinary skill in the art at the time of the invention to locally administer heparinase enzymes taught by Hoogewerf et al., Gilat et al. (1995), Vlodavsky et al., and the '772, the '641, and the '417 patents with the expectation that inflammatory responses would be decreased as taught by the '641 and '417 patents, Nash et al., and Lider et al. Based upon the teachings of Lider et al., one skilled in the art would expect that administration of heparinase would result in decreased levels of TNF α which would result in a decrease in inflammatory process mediated by TNF α. One with skill in the art would also expect that administration of heparinase would decrease chronic inflammation process since Nash et al. teaches that angiogenesis (neovascularization) is required for progression of chronic inflammation and the '417 patent discloses that Heparinases I and III inhibit neovascularization *in vivo*. Further, one with skill in the art would be motivated to administer heparinase as a treatment for ischemia/reperfusion injury because it would be expected that administration of heparinase would decrease inflammation because Gilat et al. (1994) teaches that adherent chemokines which mediate inflammation can be released by heparinase. Therefore one with ordinary skill in the art at the time of the invention would be motivated to administer heparinase I or III as a method for the treatment of inflammation (ischemia/reperfusion injury) with the expectation that angiogenesis would be inhibited and inflammation would be decreased and with the expectation that the loss of adherent chemokines would cause the decrease of the inflammatory process which they mediate, as taught by Gilat et al. (1994).

Page 1 of the specification discloses that an inflammatory response is (a) local response to cellular injury that is marked by capillary dilation, leukocytic infiltration, redness, hear and pain. The specification on page 1 further discloses that inflammatory responses can include ischemia/reperfusion injury following myocardial infarction, shock, stroke, organ transplantation, allograft rejection, rheumatoid arthritis, asthma, allergic rhinitis and glomerulonephritis. Therefore, based upon the teachings of the '641 patent, one with ordinary skill in the art would be motivated to administer heparinase to ameliorate inflammatory response that results from ischemic disease, transplantation, or stroke.

Applicant's arguments have been fully considered but have not been found persuasive, essentially for the reasons set forth in Paper No.19. Applicant argues that the references do not teach neutrophil transmigration through the vascular endothelium, that while the '641 patent teaches the use of heparinase to promote wound healing, it does not teach the use of heparinase to treat ischemia/reperfusion injury, that the previous office action did not properly apply the primary references to the Ratner et al. or Gilat et al. as secondary references, and that the Ratner et al. reference teaches away from the claimed invention. As to the argument that the references do not teach neutrophil transmigration through the vascular endothelium, page 1 of the specification describes inflammation as the recruitment of leukocytes (thus including neutrophils) to the tissue (thus transmigration through the vascular endothelium). Therefore, transmigration of neutrophils through the vascular endothelium would be an expected property of the inflammation taught by all the references. As to the argument that the '641 patent teaches the use of heparinase to promote wound healing, as previously stated, inflammation is an expected property of wound healing and a method for treating ischemia/reperfusion injury is not patentably distinct from a method for promoting wound healing. Additionally, absent evidence to the contrary, a method for treating wound healing would be expected to suggest a method for treating inflammation and thus render it obvious. As to the improper application of the Ratner et al. and Gilat et al. references, the rejection has been rewritten so as to properly include the Gilat et al. reference and the Ratner et al. reference has been withdrawn from the rejection.

9. The advisory action issued Dec. 10, 1998 indicates that the declaration filed Nov. 23, 1998 is sufficient to establish that the invention was conceived and reduced to practice prior to publications of Gilat et al. (1995), Gilat et al. (1994), Hoogewerf et al., and Lider et al. **However, upon further consideration this position is vacated.** The declaration filed Nov. 23, 1998 established that heparinase inhibits neutrophil migration *in vitro*. It does not establish that administration of heparinase *in vivo* inhibits localized inflammation. Inflammation is a complex, multifaceted process which involves many different cell types, i.e., macrophages, neutrophils, endothelial cells, and lymphocytes, as well as angiogenesis, erythema and tissue healing (see Guyton, page 848-371). The ability of heparinase to inhibit neutrophil migration *in vitro* does not establish that administration of

heparinase *in vivo* is effective in decreasing localized inflammatory responses.

Applicant's response that the teaching that administration of the '641 patent that administration of heparinase is useful to promote neovascularization does not suggest that administration of heparinase enzyme would be useful to decrease localized inflammation is not persuasive. The '641 patent clearly teaches that FGF is released by addition of heparinase to ECM which promotes wound healing. The '641 patent also discloses but does not exemplify that administration of heparinase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and **peripheral ischemic disease**, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular). Therefore, one with skill in the art at the time of the invention would have been motivated to administration heparinase locally with the expectation that it would decrease inflammation and promote wound healing.

Applicant argues that the '417 patent is in direct contradiction to the '641 patent because it teaches that heparinase enzymes are useful to inhibit angiogenesis. However, as discussed supra, inflammation is a complex, multifaceted process which takes places over a number of days and weeks. Nash et al. teaches that angiogenesis is required for the progression of chronic inflammation and agents that alter it can affect the development of inflammation and the consequent tissue destruction (see abstract, in particular). Page 1 of the specification defines an inflammatory response as a local response to cellular injury that is marked by capillary dilation, leukocytic infiltration, redness, heat and pain. Thus, Applicant's definition of the inflammatory response encompasses inflammatory responses such as transplantation, diabetes, hypertension, cerebral and peripheral ischemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus. The '641 patent clearly teaches that administration of heparinase causes the release of angiogenic endothelial cell growth factor such as FGF and that addition of heparinase may provide an effective method to mobilize and activate FGF. The '641 patent further teaches that conditions which are likely to benefit from neovascularization promoted of FGF include transplantation, diabetes, hypertension, cerebral and **peripheral ischemic disease**, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular).

Applicant's argument that the references in combination do not teach the claimed invention is not persuasive. One with skill in the art would be motivated to administer heparinase to patients with the expectation that heparinase would inhibit TNF α secretion which would lead to a decrease in inflammation for the reasons taught by Lider et al. One with ordinary skill in the art would have been motivated to administer heparinase locally with the expectation that it would inhibit

angiogenesis (neovascularization) which would inhibit chronic inflammation as taught by Nash et al.

10. Claims 1-7 and 18-19 are directed to an invention not patentably distinct from claim of commonly assigned U.S. Patent No. 5,997,863. Specifically, Claims 1-9 the '863 patent are drawn to methods of enhancing normal would healing by administering heparinase 2, heparinase 3, and heparinase from *Flavobacterium* HP206. Wound healing includes and cannot be separated from an inflammatory response, since inflammatory cells, such as neutrophils, participate in wound healing and many of the "inflammatory cytokines", i.e. TNF-α, participate in wound healing. The specification of the '863 patent discloses that would healing is generally divided into three temporally overlapping phases: inflammation, proliferation and remodeling (see column 2, lines 56-65, in particular).

Commonly assigned U.S. Patent No. 5,997,863, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78© and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 and 18-19 are rejected under the judicially created doctrine of obvious-type double patenting over claims 1-10 of the '863 patent. The conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '863 patent pertain to method of treating wounds by administering heparinase. Wound healing is a type of inflammatory response as described, supra.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt in Art Unit 1644 whose telephone number is (703) 308-9805. The examiner can normally be reached on Monday through Thursday and alternate Fridays from 7:45 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973 The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

G.R. Ewoldt, Ph.D.
Examiner
Tech Center 1600
July, 28 2000

Christina Chan
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